UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/576,785	04/21/2006	Tao Cheng	060230PCTUS	5925

26285 7590 01/13/2010

K&L GATES LLP
535 SMITHFIELD STREET
PITTSBURGH, PA 15222

EXAMINER	
FORD, ALLISON M	
ART UNIT	PAPER NUMBER
1651	
MAIL DATE	DELIVERY MODE
01/13/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/576,785	CHENG, TAO	
	Examiner	Art Unit	
	ALLISON M. FORD	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 November 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,6,7,23,24,26,27 and 29-39* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,6,7,23,24,26,27 and 29-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 11/2/09 has been entered.

Claims 1, 2, 6, 7, 23, 24, 26 and 27 have been amended; new claims 29-39 have been added. Claims 1, 2, 6, 7, 23, 24, 26, 27 and 29-39 are currently pending in the instant application, all of which have been considered on the merits.

All arguments have been fully considered, and will be addressed below, as appropriate. Rejections/objections not repeated herein have been withdrawn.

Priority

The instant application is a national stage entry under 35 USC 371 of international application PCT/US04/35220 (filed 10/25/2004), which claims priority under 35 USC 119(e) to US provisional applications 60/514,329 (filed 10/24/2003) and 60/620,154 (filed 10/19/2004).

However, the disclosure of the prior-filed application, Application No. 60/514,329, fails to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35

U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

Provisional application 60/514,329 fails to provide support for the method of delivering small RNA interfering sequences (siRNA) to stem cells for the reduction of p18 levels in the intracellular environment of the stem cells, which step is required by all claims of the instant application. The disclosure of 60/514,329 does disclose that the absence of p18 causes enhanced potential of self-renewal leading to an expansion of HSCs and multipotent HPCs, and suggests that down-modulating p18 may allow enhanced stem-cell expansion (self-renewal), but fails to provide any support for a step of actively down-modulating p18 levels in wild-type cells, and fails to disclose or suggest use of siRNA. Therefore, the effective filing date for all claims of the instant application is considered to be 10/19/2004, the filing date of the later provisional application 60/620,154. Prior art has been applied accordingly.

Specification

The amendment to the specification has been entered. The amendment obviates the previous objection thereto.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Applicants have amended claim 1 to limit the method to *promoting* self-renewal of stem cells.

The amendment to claim 1 obviates the ground of rejection over claims 1-2 and 6-7 (3 and 8 now being cancelled) as failing to provide enablement for the full scope of *controlling* self-renewal of stem cells.

Applicants have traversed the rejection of record under 35 USC 112, first paragraph, as failing to provide enablement for the full scope of *stem cells*, as opposed to just *hematopoietic stem cells*, whose self-renewal may be promoted/stimulated by the instant inventive method. The traversal is on the grounds that the specification discloses "[d]ownmodulation of p18 may permit enhanced stem cell expansion in vitro," and teaches that "[g]iven the non-specific expression of p18 in hematopoietic cells, this approach can also be applied to other stem cells in the body." Applicants further argue the specification teaches (i) p18 acts as an inhibitor at early G1-phase of the cell cycle, (ii) that all adult human stem cells go through the four distinct phases of the cell cycle, and thus (iii) p18 normally acts as an inhibitor at the early G1-phase for all types of adult stem cells. Applicants assert that from this information one having ordinary skill in the art would have had a reasonable expectation that reducing intracellular p18 levels in any type of stem cell would effectively *un*-inhibit (i.e. promote/stimulate) entry of any stem cell into the G1 phase of the cell cycle (wherein entry into the cell cycle will ultimately result in stem cell self-renewal), and thus practice of the invention with any type of stem cell would not have required undue experimentation.

Applicants' arguments have been fully considered, but are not found persuasive.

It is acknowledged that the specification *discloses* the invention as claimed, specifically asserting that downmodulation of p18 can be applied to other stem cells in the body to enhance stem cell expansion in vitro; however the claims stand rejected because this statement is not supported by evidence or data of record, nor by the teachings in the art at the time of filing. Similarly, while the statements that (i) p18 acts as an inhibitor at early G1-phase of the cell cycle, and (ii) that all adult human stem cells go through the four distinct phases of the cell cycle, are supported by the teachings in the art, the conclusion that (iii) p18 normally acts as an inhibitor at the early G1-phase for *all types of adult stem cells*, is not supported by evidence or data of record, nor by the teachings in the art. In fact, there was evidence in the art that

suggests that p18 does *not* play a role in differentiation of all adult stem cells: Franklin et al report that p18-null mice showed normal myogenesis and adipogenesis, indicating that p18 does not have an essential role in causing cell cycle withdrawal during the differentiation of muscle and adipose tissue (See Franklin et al, Genes & Development, 1998, Pg. 2900, col. 2, last full paragraph). Muscle and adipose tissue are mesenchymal stem cell-derived tissues, thus the report in Franklin et al that loss of p18 did *not* affect myogenesis and adipogenesis contradicts the conclusion that p18 normally acts as an inhibitor at the early G1-phase for *all types of adult stem cells*. Therefore the rejection of record stands (modified as necessary by claim amendments and claim additions).

Claims 1, 2, 6, 7, 23, 24, 26, 27, 30, 32, 33, 35 and 37-39 stand rejected under 35 U.S.C. 112, first paragraph, as failing to provide enablement for the full scope of the claimed invention. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicant's specification is found enabling for promoting/stimulating self-renewal of a population of hematopoietic stem cells (HSCs) by reducing intracellular levels of p18 through use of siRNA sequences targeting the p18 mRNA delivered to the HSCs

Applicant's specification is not found to be enabling for promoting/stimulating self-renewal of a population of *any stem cell* by reducing intracellular levels of p18 through use of siRNA sequences. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to carry out the method of the invention commensurate in scope with the current claims.

Analysis of whether a particular claim is supported by the disclosure in an application requires a determination of whether that disclosure, when filed, contained sufficient information regarding the subject matter of the claims as to enable one skilled in the pertinent art to make and use the claimed

invention without undue or unreasonable experimentation. See *Mineral Separation v. Hyde*, 242 U.S. 261, 270 (1916). The key word is 'undue,' not experimentation.' " (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all these factors are considered, a sufficient number are discussed below so as to create a prima facie case.

Applicants' claims are directed to promoting (claims 1 and 39) or stimulating (claim 23) the self-renewal of a population of human stem cells by reducing intracellular levels of p18 through use of siRNA targeting the p18 mRNA.

The current independent claims encompass all types of stem cells. Thus the breadth of the claims 1, 6, 23, 26, 33, 38 and 39 include promoting/stimulating self-renewal of a population of any type of stem cell, including embryonic stem cells and adult stem cells, including pluripotent stem cells, like mesenchymal stem cells and hematopoietic stem cells, as well as lineage specific stem and progenitor cells, such as neural stem cells, epithelial stem cells, hair follicle progenitor cells, and more.

Claims 2, 7, 24, 27, 30, 32, 35 and 37 limit the stem cells to *adult* stem cells. Thus the breadth of claims 2, 7, 24, 27, 30, 32, 35 and 37 include promoting/stimulating self-renewal of a population of any type of adult stem cell, including pluripotent stem cells, like mesenchymal stem cells and hematopoietic stem cells, as well as lineage specific stem and progenitor cells, such as neural stem cells, epithelial stem cells, hair follicle progenitor cells, and more.

With regards to predictability in the art in the field of promoting self-renewal of stem cells, in general, promoting self-renewal of any adult stem cell was unpredictable, at best (See, e.g. Deans et al,

Experimental Hematology, 2000 and. Nakauchi et al, Annals of the NY Acad Sciences, 2001). Yet the claims more specifically require the increased self-renewal to be achieved by a reduction in intracellular level of p18. Understanding of the role of p18 in cell growth and development was nascent at the time of filing, the p18 gene only being identified in 1994 (Guan et al, Genes & Development, 1994). While p18 was considered to play a role in multiple cell types (See Franklin et al, Genes & Development, 1998), only its role in hematopoietic cells was well understood (See Sherr et al). Work by Sherr et al identified p18 functions as a 'brake' in the G1→S transition of HSCs (See Sherr et al, col. 4, ln 46-54); thus elimination of the p18 protein resulted in increased proliferation (See Sherr et al, col. 5, ln 11-18). Therefore, the art, like the instant application, supports the role of p18 in hematopoiesis, and specifically that suppression of the p18 results in increased proliferation of HSCs (See Sherr et al, col. 5, ln 11-18).

However, at the time the invention was made the role of p18 in other cells, including non-hematopoietic stem cells, while not fully characterized, was recognized as unique to different cell types. For example, Franklin et al report that p18-null mice showed normal myogenesis and adipogenesis, indicating that p18 does not have an essential role in causing cell cycle withdrawal during the differentiation of muscle and adipose tissue (See Franklin et al, Genes & Development, 1998, Pg. 2900, col. 2, last full paragraph). Yet p18-null mice did have enlarged hematolymphoid organs compared to wild-type p18 mice; Franklin et al explain the enlarged thymus and spleen were due to increased proliferation rate of T-lymphocytes and B-lymphocytes, respectively, due to loss of p18 (See Franklin et al, *Id*, Pg. 2902, 1st full paragraph in second column- Pg. 2903,1st full paragraph). Thus, though the role of p18 was not fully characterized for all cell types, there was evidence in the art that the p18 had different affects on cell cycling of different cell types. It is particularly noted that muscle and adipose tissue are mesenchymal stem cell-derived tissues, thus the report in Franklin et al that loss of p18 did *not* affect myogenesis and adipogenesis supports the holding that the correlation between reduction of intracellular p18 levels and promotion/stimulation of self-renewal stem cells is not true for all stem cells,

as it does not affect mesenchymal stem cells. Thus there was, at least, a recognized level of unpredictability with regards to the effect of modulation of the p18 levels in other cell types, specifically other stem cell types.

The specification does provide evidence that $p18^{-/-}$ HSCs exhibit increased self-renewal as compared to non-treated cells (See, e.g. Figure 9). The specification further provides evidence that intracellular p18 levels can be reduced in murine and human HSCs (See, e.g. Figure 12b). Therefore, the specification is found enabling for a method of promoting self-renewal of HSCs by reducing the p18 level through siRNA sequences. There are no examples of reduced p18 levels in any other type of stem cell resulting in increased self-renewal. Guidance and teachings provided by the Applicant regarding applicability of the method to non-HSC stem cells is limited to a statement that "[G]iven the non-specific expression of p18 in hematopoietic cells, this approach can also be applied to other stem cells types in the body" (See Spec at Pg. 4, lines 1-2).

Due to the lack of teachings in the art regarding the role of p18 in stem cells beside HSCs, and the recognized unpredictability in the area of controlling stem cell differentiation & self-renewal, a large amount of guidance and teachings would be necessary in order to be enabling for controlling self-renewal of all stem cell types by reducing intracellular p18 levels; however, as discussed above, the instant specification fails to provide such teaching and guidance. The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). Thus, due to the high level of unpredictability in the art, the current specification would have to provide greater amounts of teachings and guidance directed to methods of carrying out the claimed invention. A large amount of undue experimentation would be required to determine the parameters and additional conditions (in addition to reduction of p18 levels) necessary to successfully promote self-renewal of all stem cells, or if such can even be achieved.

Therefore, due to the sum of all the aforementioned factors, one of ordinary skill in the art, at the time the invention was made, would not expect success carrying out the method of promoting self-renewal of any type of stem cell except for HSCs by reducing intracellular p18 levels. Given that the art fails to recognize and Applicant has failed to demonstrate that any species of stem cell, besides HSCs, will exhibit enhanced self-renewal upon reduction of intracellular p18 levels, the skilled artisan would be faced with the impermissible burden of undue experimentation in order to practice the claimed invention on any species of stem cell. Accordingly, claims 1, 2, 6, 7, 23, 24, 26, 27, 30, 32, 33, 35 and 37-39 are deemed properly rejected.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The claim amendments have obviated the grounds of rejection previously made under 35 USC 112, second paragraph, as being indefinite.

The following new grounds of rejection are set forth:

Claim 39 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 39 reads, "The method of promoting self-renewal of a population of human stem cells…" It is unclear if claim 39 is intended to depend from a previous claim, or if it is to be an independent claim. If claim 39 is to depend from a previous claim, it must be made clear which previous claim; if claim 39 is to be an independent claim the preamble should be amended to recite "A method of promoting...." Correction is required.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Applicants have traversed the rejections under 35 USC 103(a) on the grounds that the Examiner has failed to clearly articulate the reason one having ordinary skill in the art would have found the invention, as claimed, obvious. This argument is based on Applicants' interpretation that none of Sherr, Bertrand, An or Walters teach or suggest *self-renewal* of hematopoietic stem cells through reduction of intracellular p18 levels, but rather that Sherr only teaches *proliferation* of hematopoietic stem cells. Applicants assert in *stem cell biology* stem cell proliferation refers to cell division and differentiation of stem cells into progenitor cells, whereas s*tem cell self-renewal* results in either one stem cell becoming two stem cells or one stem cell becoming one stem cell and one progenitor cell. Applicants further traverse the rejection of record on the grounds that antisense oligonucleotides and siRNA are not functional equivalents with respect to gene silencing, as asserted in the rejection. Applicants argue that siRNA has much more potent gene silencing activity than antisense oligonucleotides; and thus Applicants assert siRNA may not have been routinely substituted for the antisense oligonucleotides in the method of Sherr for the predictable result of achieving reduction in intracellular p18 levels to result in self-renewal of the HSCs of Sherr. Applicants assert that substitution of siRNA for the antisense oligonucleotides of Sherr would have actually been expected to have been detrimental to the method of Sherr, which Applicants assert was intended to reduce intracellular p18 levels to only promote *proliferation* (in a sense that included differentiation) of HSCs, whereas use of siRNA would have been expected to completely block p18 expression, thereby promoting *self-renewal* of the HSCs.

Applicants' arguments have been fully considered, and are found persuasive. Specifically, upon review, it is conceded that the disclosure of Sherr cannot be held to unequivocally suggest that proliferation of HSCs equates to proliferation *in an undifferentiated state* (i.e. self-renewal). Sherr only teach inhibition of p18 levels in cells in need of 'growth stimulation' (See Sherr col, 16, ln 61-64). Sherr does teach that cells in need of 'growth stimulation' may include stem cells, including HSCs, but they do not specify that the growth stimulation may be in the form of self-renewal. In contrast, Sherr states that HSCs are maintained in a non-cycling state and that the cells enter the cell cycle (i.e. differentiate) when new blood cells are needed. Sherr goes on to suggest that the p18 and/or p19 are responsible for the maintenance of HSCs in the non-cycling state, and suggest moving HSCs into the cycling state by reducing the amount of p18 and/or p19; because Sherr state that 'causing cells to enter the cell cycle results in formation of blood cells' (i.e. differentiation), it must be interpreted that the step of reducing the amount of p18 and/or p19 would be carried out to cause the HSCs to enter the cell cycle to produce new (differentiated) blood cells. Therefore the rejection is withdrawn.

The following new grounds of rejection are made:

Claims 1, 2, 6, 7, 23, 24, 26, 27, 29, 31, 33, 34, 36, 38 and 39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yuan et al (Nature: Cell Biology, May 2004), in view of Sherr et al (US Patent 6,033,847), Largman et al (US Patent 5,837,507), Bertrand et al (Biochemical & Biophysical Research Comm, 2002), and further in view of An et al (Human Gene Therapy, 2003) and Walters et al (Antisense and Nucleic Acid Drug Development, 2002).

Yuan et al report that the absence of p18 in mouse hematopoietic stem cells (HSCs) causes enhanced potential of self-renewal leading to an expansion of HSCs and multipotent hematopoietic progenitor cells (HPCs) (both HSCs and HPCs are being considered adult hematopoietic stem cells) (See

Yuan et al, Pg. 441, col. 1, first full paragraph). Yuan et al suggest that down-modulation of p18 may allow enhanced self-renewal of stem cells (See Yuan et al, Pg. 441, col. 1, last full paragraph).

Yuan et al differ from the instant invention in that, while they show absence of p18 promotes self-renewal of mouse HSCs, and while they suggest that down-modulation of p18 may be useful in enhancing self-renewal of stem cells, they do not disclose a step of actively down-modulating p18 expression in wild-type stem cells by delivering siRNA to the stem cells. Furthermore, Yuan et al report on HSCs of mice, whereas the instant claims are drawn to manipulation of human stem cells.

However, it is submitted that one having ordinary skill in the art, having read the disclosure of Yuan et al, would have found it *prima facie* obvious to follow the suggestion of Yuan et al and actively down-modulate p18 expression in HSCs to promote HSC self-renewal. There was clear motivation in the art to devise a method by which to maintain HSCs, particularly HSCs, *in vitro* in an immature, undifferentiated state (See, e.g. Sherr et al, col. 17, ln 43-45), for example, Yuan et al demonstrate how undifferentiated mouse HSCs can reconstitute mouse hematopoietic systems after lethal irradiation. Furthermore, one would have found it *prima facie* obvious to apply the suggested method to human HSCs, for the same purpose of promoting human HSC self-renewal. Transplantation of human HSCs which have been modified to have enhanced self-renewal capacity to human patients for reconstitution of the hematopoietic system was a known therapy in the art (See, e.g. Largman et al, col. 2, ln 66- col. 3, ln 9), and is particularly useful in treatment of patients who have undergone chemotherapy (lethal irradiation).

Bertrand et al is cited for their disclosure that siRNA technology was known to effectively silence gene expression in mammalian cells (See Bertrand et al, Pg. 1000).

Sherr et al is cited for their disclosure of the gene sequence for mouse and human p18 (See Sherr et al, col. 4, ln 5-11 & SEQ ID NO: 1). Because the gene sequence for both mouse and human p18 are known, it would have been well within the purview of one having ordinary skill in the art to produce an appropriate siRNA molecule which could effectively inhibit p18 expression in mouse or human cells without undue experimentation.

Thus, for the purpose of maintaining HSCs, both mouse and human, in an undifferentiated state *in vitro*, such that they may be utilized as a means for hematopoietic reconstitution following lethal radiation, such as in chemotherapy patients, one having ordinary skill in the art would have been motivated to create and deliver siRNA molecules targeting the mouse or human p18 sequence to mouse or human HSCs, respectively. Based on the teachings of Yuan et al, one would have had a reasonable expectation that by inhibiting p18 expression in the HSCs, the HSCs will undergo self-renewal; one would have had a reasonable expectation of successfully using siRNA to effect the inhibition of p18 expression based on the teachings of Bertrand et al, that siRNA may be developed and used to inhibit expression of any mammalian gene product, so long as the gene sequence was known; Sherr et al disclose the gene sequences.

It is further noted that siRNA molecules are routinely delivered to cells through lentiviral vectors (See An et al, Pg 1228, "Lentiviral Vector Production") or by electroporation (See Walters et al, Pg 417, col. 2). Selection of either art accepted method for delivery of an siRNA molecule to the HSCs for use in the method rendered obvious by Yuan et al would therefore have been prima facie obvious to one of ordinary skill in the art, with a reasonable expectation of successfully delivering the siRNA molecule to reduce p18 expression, thereby resulting in increased self-renewal of the HSCs.

Therefore the invention of claims 1, 2, 6, 7, 23, 24, 26, 27, 29, 31, 33, 34, 36, 38 and 39, as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ALLISON M. FORD whose telephone number is (571)272-2936. The examiner can normally be reached on 8:00-6 M-Th.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Allison M. Ford/
Primary Examiner, Art Unit 1651